Consumption of meat and dairy and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition

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Key words: lymhomas, meat consumption, dairy consumption, cohort study
Grant sponsors: Europe Against Cancer Program of the European Commission (SANCO), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum, German Federal Ministry of Education and Research, Danish Cancer Society, Health Research Fund (FIS) of the Spanish Ministry of Health, Spanish Regional Governments of Andalucia, Asturia, Basque Country, Murcia and Navarra, the ISCIII Network RCESP (C03/09), ISCIII of the Spanish Ministry of Health (RETICC DR06/0020), Spain, Cancer Research UK, Medical Research Council, United Kingdom, Greek Ministry of Health, Stavros Niarchos Foundation and Hellenic Health Foundation, Greece, Italian Association for Research on Cancer (AIRC), Italian National Research Council, Fondazione-Istituto Banco Napoli, Italy, Compagnia di San Paolo, Dutch Ministry of Public Health, Welfare and Sports, Dutch Prevention Funds, LK Research Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund, Swedish Cancer Society, Swedish Scientific Council, Regional Government of Skåne, Sweden, Norwegian Cancer Society, Research Council of Norway, Nordforsk, French League against Cancer (LNCC), National Institute for Health and Medical Research (INSERM), France, Mutuelle Générale de l'Education Nationale (MGEN), France, 3M Co, France, Gustave Roussy Institute (IGR), France, General Councils of France

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The consumption of meat and other foods of animal origin is a risk factor for several types of cancer, but the results for lymphomas are inconclusive. Therefore, we examined these associations among 411,097 participants of the European Prospective Investigation into Cancer and Nutrition. During a median follow-up of 8.5 years, 1,334 lymphomas (1,267 non-Hodgkin lymphoma (NHL) and 67 Hodgkin lymphomas) were identified. Consumption of red and processed meat, poultry, milk and dairy products was assessed by dietary questionnaires. Cox proportional hazard regression was used to evaluate the association of the consumption of these food groups with lymphoma risk. Overall, the consumption of foods of animal origin was not associated with an increased risk of NHLS or HL, but the associations with specific subgroups of NHL entities were noted. A high intake of processed meat was associated with an increased risk of B-cell chronic lymphocytic leukemia (BCLL) [relative risk (RR) per 50 g intake = 1.31, 95% confidence interval (CI) 1.06–1.63], but a decreased risk of follicular lymphomas (FL) (RR = 0.58; CI 0.38–0.89). A high intake of poultry was related to an increased risk of B-cell lymphomas (RR = 1.22; CI 1.05–1.42 per 10 g intake), FL (RR = 1.65; CI 1.18–2.32) and BCLL (RR = 1.54; CI 1.18–2.01) in the continuous models. In conclusion, no consistent associations between red and processed meat consumption and lymphoma risk were observed, but we found that the consumption of poultry was related to an increased risk of B-cell lymphomas. Chance is a plausible explanation of the observed associations, which need to be confirmed in further studies.

Lymphomas are a heterogeneous group of malignancies that arise from the lymphatic system and are usually classified into Hodgkin lymphomas (HLs) and non-HL (NHL). During the past decades, an increase in the incidence of NHL has been observed in many countries until about the year 2000,[1] and a change in lifestyle might be one possible explanation for this increase. During the past years, meat consumption has been found to be associated with several types of cancer[2]; especially red and processed meat consumption seem to increase the risk of colorectal cancer[3] and gastric cancer.[4] Some studies already examined the association between meat consumption and the risk of lymphoma, but the results of these studies are quite inconsistent, with some showing an increased risk of NHL with increasing red meat consumption[5–9] and others showing no association.[10–18] Similarly, the results are diverse for other animal products, that is, poultry[5–7,9,11,13,18,19] and for milk and milk product consumption.[5–7,9,12–16] Most of these studies are case-control studies, which may be prone to selection and recall bias.

The European Prospective Investigation into Cancer and Nutrition (EPIC) provides the opportunity to examine the association of the consumption of foods of animal origin such as meat and dairy products and lymphoma risk in a prospective design and a population with a wide spectrum of dietary habits.

Material and Methods

Population

EPIC is a large prospective cohort study conducted since 1992 in 23 centers in 10 European countries [Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), United Kingdom (Cambridge and Oxford), Greece, Italy (Florence, Varese, Ragusa, Turin and Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra and San Sebastian), Sweden (Malmö and Umea) and The Netherlands (Bilthoven and Utrecht)]. In most centers, the participants were recruited from the general population. However, French participants were female members of a health insurance for school and university employees. Spanish and Italian participants were recruited among blood donors, members of several health insurance programs, employees of several enterprises, civil servants and also the general population. In Utrecht and Florence, participants in mammographic screening programs were recruited for the study. In Oxford, half of the cohort consisted of "health conscious" subjects from England, Wales, Scotland and Northern Ireland, which includes a high percentage of vegans, ovo-lacto vegetarians, fish eaters (consuming fish but no meat) and meat eaters. The cohorts of France, Norway, Utrecht and Naples include women only.[20]

The EPIC cohort consists of 521,448 participants. Of these, we excluded prevalent cancer cases (n = 23,633), subjects with missing follow-up information (n = 3,447), with incomplete dietary (n = 6,159), nondietary (n = 60) or with a ratio for energy intake *versus* energy expenditure in the top and bottom 1% (n = 9,674). We also excluded 14 unclear lymphoma cases and the French cohort because lymphoma cases have not been ascertained fully (n = 68,050). Thus, the current analysis was based on 410,411 EPIC participants among whom 1,334 incident lymphoma cases occurred.

Table 1. Frequency of lymphomas and lymphoma subgroups by country in EPIC

			NHL subgroups					B-cell lymphoma subgroups					
	Person-years	Lymphomas	NHL	HL	B-cell lymphomas	T-cell lymphomas	NHL NOS	DLBCL	FL	BCLL	MM	Other	B NOS
Italy	383,603	132	126	6	113	9	4	14	23	17	28	12	4
Spain	401,696	111	100	11	92	5	3	18	15	22	21	5	1
UK	645,690	255	245	10	215	6	24	29	26	38	55	37	20
Netherlands	316,547	91	89	2	83	4	2	17	16	15	20	9	10
Greece	183,538	36	33	3	31	1	1	4	3	9	7	6	1
Germany	410,425	124	116	8	104	5	7	9	13	23	33	15	7
Sweden	517,081	289	278	11	230	5	43	15	15	40	77	66	64
Denmark	421,076	251	238	13	220	7	11	48	24	65	44	19	18
Norway	213,027	45	42	3	40	2	0	5	5	5	7	13	10
Total	3492,683	1334	1267	67	1128	44	95	159	140	234	292	182	135

HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma (including Burkitt); FL, follicular lymphoma (all grades); BCLL, B-cell chronic lymphatic leukemia (including small lymphocytic leukemia and prolymphocytic lymphocytic leukemia); MM, multiple myeloma/plasmacytoma; Other, other specified subgroups: BALL, B-cell acute lymphatic leukemia (including ALL); LPL, lymphoplasmocytic lymphoma/Waldenstroem disease; ML, marginal zone B-cell lymphoma; BO, B-cell lymphoma, other.

Exposure assessment

Diet over the previous 12 months was assessed using dietary assessment instruments that were specifically developed for each participating country based on a common core protocol.[20] Questions were structured by meals on the questionnaires used in Italy, Spain and Malmö (Sweden) and by foods and/or food groups in the other centers. Participants were asked to report their average consumption of each food item over the previous 12 months, according to the precoded categories ranging from never or less than once per month to six or more times per day. Individual average portions were estimated in France, Germany, Greece, Italy, The Netherlands and Spain, whereas standard portions were assigned to all subjects in Denmark, United Kingdom, Norway and Umeå, and a combination of methods for estimating portion size was used in Malmo. All dietary measurement instruments have been validated previously in a series of studies within the various source populations participating in EPIC.[21]

The food groups red meat, processed meat, poultry, offals, eggs, milk (milk and milk beverages), cheese and yogurt were included in the analysis (see Appendix). Lifestyle questionnaires were used to collect information on education, medical history, tobacco and alcohol consumption and physical activity. Height and weight were measured at the baseline examination, except for Norway and Oxford, where height and weight were self-reported.[20]

Outcome assessment

Cancer diagnoses were based on the population registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden, United Kingdom. An active follow-up through study subjects and next-to-kin information, the use of health insurance records and cancer and pathology registries were used in Germany and Greece. Mortality data were also obtained from either the cancer or the mortality registries at the regional or national level. Cancer cases were identified by the end of the censoring periods ending between December 2002 and December 2005 in the EPIC centers, besides Germany and Greece, where the end of the follow-up was considered to be the last known contact, date of diagnosis or date of death, whichever came first. Currently, vital status is known for 98.4% of all EPIC subjects.

The diagnosis of lymphoma cases was based on the second revision of the International Classification of Diseases for Oncology (ICD-O-2). We reclassified cases into ICD-O-3, which is based on the World Health Organisation (WHO) 2001 classification,[22] using a conversion program available on the web site of the Surveillance Epidemiology and End Results (SEER) programme (http://seer.cancer.gov/tools/conversion/ICD02-3manual.pdf) and involving a pathology expert and experts from the EPIC centers. Because not all ICD-O-2 diagnostics can be translated unequivocally into a lymphoma diagnosis according to the WHO classification, we left the respective lymphomas unclassified (not otherwise specified "NOS") when further detailed specification failed (17.2%). The majority of these unclassified cases have already been unclassified according to the ICD-O-2 classification in the original EPIC database.

In the current analysis, the following groups were considered: HL and NHL; within NHL, B-cell lymphoma and T-cell lymphoma, and among B-cell lymphomas, the entities diffuse large B-cell lymphomas (DLBCL), follicular lymphomas (FL), B-cell chronic lymphocytic leukemia (BCLL) and multiple myeloma (MM)/plasmocytoma. Other entities were not considered because of small numbers (Table 1).

Statistical analysis

Cox proportional hazards regression was used to examine the association of meat, egg and dairy consumption with

lymphomas entering food consumption as categorical variables by quartiles of intake into the models. Age was used as the primary time variable in the Cox models. Time at entry was age at recruitment, exit time was age when participants were diagnosed with cancer, died, were lost to follow-up or were censored at the end of the follow-up period, whichever came first. The analyses were stratified by center, gender and age at recruitment in 1-year categories. In our regression models, we adjusted for cigarette smoking [never, former (quit $<$ 10 years ago and quit $\geq$ 10 years ago), current ($<$15 cigarettes/day, 15–24 cigarettes/day and $\geq$25 cigarettes/day), other and missing], education (no degree or primary school completed, technical or professional school completed, secondary school completed, university degree, not specified or missing), alcohol consumption at baseline, fruit intake, vegetable intake and energy intake (all continuous). Height, weight and physical activity did not alter the associations and were not included in the final Cox regression models. Trend tests were performed by assigning a score ranging from 1 to 4 according to a participant's quartile of intake of the respective food item as a continuous variable into the Cox regression model.

To correct for measurement error and improve the comparability of dietary data across the participating centers, dietary intakes calculated from questionnaire data were calibrated with 24-hour dietary recall data from an 8% random sample cohort. A fixed-effects linear model was used in which center and sex-specific recall data were regressed on the food frequency questionnaire (FFQ) intakes.[23–26] Non-consumers of a specific food group were excluded from the regression calibration models and kept as zero values. Calibrated and uncalibrated data were used to estimate the association of meat, egg, milk and dairy consumption with lymphoma risk on a continuous scale.

For B-cell lymphomas, MM, BCLL and DLBCL (*i.e.*, most frequent lymphoma groups), we tested for interaction by sex by including a cross-product term along with the main effect terms in the Cox regression model. The statistical significance of the cross-product term was evaluated using the likelihood ratio test. We also examined whether the association was altered by excluding the first 2 years of follow-up. Finally, heterogeneity between level of education and countries was assessed using likelihood chi-square tests. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results

During follow-up, 1,334 lymphoma cases (NHL: n = 1267; HL: n = 67) were diagnosed. Among NHL, 89% were B-cell lymphoma. A detailed distribution of cases by lymphoma subentity, country and sex is displayed in Table 1.

Baseline characteristics of the study participants are shown in Table 2 for the top and bottom categories of red and processed meat, poultry and milk consumption. As expected, energy intake was always highest in the top category of intake. Fruit and vegetable intake was lower in the top quintile of red and processed meat intake but higher in the top category of poultry intake. We observed differences in the percentage of smokers and highest level of education by meat, poultry and milk consumption habits, which were most pronounced for meat.

Overall, we did not observe a statistically significant association of red or processed meat consumption with risk of HL, T-cell lymphoma or B-cell lymphoma (Tables 3 and 5). We observed an increase in BCLL risk by consumption of processed meat [relative risk (RR) = 2.19, 95% confidence interval (CI) 1.27–3.77, fifth *vs.* first quintile (Table 4); RR = 1.75, 95% CI 1.11–2.75) per 50 g intake in the calibrated model, (Table 6)]. In contrast, processed meat intake was inversely associated with the risk of FL in the categorical (Table 4) and the continuous model (Table 6). In the continuous models, we observed statistically significant heterogeneity in the associations between processed meat intake and lymphoma risk between subentities of B-cell lymphomas (p-heterogeneity $<$ 0.05).

Poultry consumption was associated with an increased risk of NHL (RR per 10 g intake/day = 1.56, 95% CI 1.26–1.94 in the calibrated continuous model; Table 5), B-cell lymphoma (RR = 1.64, 95% CI 1.27–2.11, Table 5), FL (RR = 3.80, 95% CI 1.32–10.91, Table 6) and BCLL (RR = 2.60, 95% CI 1.56–4.36, Table 6) in the continuous and categorical models (Tables 3 and 4). No consistent associations with the risk of HL, NHL or any NHL subentity were found for the consumption of offals and eggs (Tables 3–6).

No consistent associations between consumption of milk and dairy products with risk of NHL and B-cell lymphoma were observed (Tables 3 and 5). A high consumption of milk, that is, a daily intake of $\geq$400 g/day was inversely associated with the risk of FL [RR = 0.51 (0.29–0.90)] and MM [RR = 0.74 (0.52–1.07), Table 4]; the continuous trend tests also suggested inverse associations although they were not statistically significant. Cheese and yoghurt consumption were not associated significantly with lymphoma risk (Tables 3–6).

Subgroup analyses

The associations of food intake and risk of B-cell lymphomas, DLBCL, BCLL and MM were not modified by sex (all $p >$ 0.05). Excluding first 2 years of follow-up from the analyses did not materially alter the observed associations (data not shown). Heterogeneity by country was not detected besides for the association between poultry consumption and risk of B-cell lymphoma (p-heterogeneity = 0.03). This heterogeneity was due to a nonsignificantly inverse association between poultry consumption and risk of B-cell lymphoma in the Swedish cohort (RR = 0.67; 95% CI 0.39–1.13). After excluding the Swedish cohort from the analysis, the p value for heterogeneity was 0.94.

Table 2. Baseline characteristics of EPIC study participants by consumption of foods of animal origin

		Categories of red and processed meat intake		Categories of poultry intake		Categories of milk intake	
	Total cohort	Category 1 (<20 g/day)	Category 5 (≥80 g/day)	Category 1 (<10 g/day)	Category 5 (≥40 g/day)	Category 1 (<100 g/day)	Category 5 (≥400 g/day)
Men							
Age at recruitment (yr)	52.7 (45.7–59.6)	50.4 (41.1–60.1)	52.4 (46.4–57.6)	51.7 (43.6–59.8)	53.0 (46.7–59.6)	52.4 (45.7–58.8)	53.2 (46.3–60.1)
Total energy intake (kcal/day)	2352 (1944–2823)	1935 (1595–2352)	2929 (2521–3407)	2204 (1811–2659)	2521 (2079–3024)	2265 (1870–2731)	2523 (2111–2997)
Alcohol intake (g/day)	13.0 (4.0–30.3)	7.3 (1.5–17.8)	20.8 (8.1–44.0)	9.8 (2.9–24.1)	13.7 (3.9–33.7)	17.5 (5.9–37.7)	8.5 (2.2–20.5)
Vegetable intake (g/day)	151 (94–247)	207 (119–325)	150 (101–224)	119 (71–198)	215 (143–315)	144 (92–248)	146 (87–227)
Fruit intake (g/day)	155 (80–288)	200 (105–351)	131 (65–241)	129 (69–238)	205 (105–353)	154 (77–311)	138 (71–240)
BMI at baseline (kg/m^2)	26.1 (24.0–28.6)	24.9 (22.9–27.3)	26.8 (24.5–29.4)	25.6 (23.5–28.0)	26.7 (24.6–29.2)	26.4 (24.2–28.9)	25.7 (23.7–28.2)
Smoking							
Never	32.9	42.9	26.5	36.7	32.4	29.7	36.2
Former	36.3	36.8	34.0	34.9	38.7	38.2	33.2
Current	29.4	18.3	39.0	27.2	27.0	31.0	29.0
Education							
Primary school completed	27.1	16.1	33.6	25.8	27.7	26.9	28.1
University degree	26.5	38.0	22.2	29.9	22.2	27.2	25.2
Women							
Age at recruitment (yr)	50.8 (43.4–57.5)	49.6 (40.2–57.3)	50.7 (43.5–56.7)	50.1 (41.6–57.2)	51.4 (44.2–58.4)	50.6 (43.6–56.7)	52.2 (44.2–59.4)
Total energy intake (kcal/day)	1827 (1516–2193)	1643 (1350–1982)	2485 (2137–2903)	1735 (1436–2079)	1993 (1662–2386)	1714 (1416–2069)	2033 (1723–2395)
Alcohol intake (g/day)	2.9 (0.4–10.0)	2.4 (0.4–8.9)	4.4 (0.6–12.9)	2.8 (0.5–9.5)	2.7 (0.4–10.2)	3.2 (0.6–10.8)	2.6 (0.4–9.3)
Vegetable intake (g/day)	166 (108–259)	200 (120–311)	174 (118–255)	144 (94–231)	239 (164–335)	153 (101–246)	175 (114–265)
Fruit intake (g/day)	202 (114–326)	227 (126–361)	182 (98–296)	180 (101–289)	249 (146–380)	189 (101–325)	208 (122–318)
BMI at baseline (kg/m^2)	24.6 (22.3–27.8)	23.7 (21.5–26.8)	26.2 (23.3–30.0)	23.9 (21.7–26.8)	25.7 (23.1–29.2)	24.7 (22.2–27.9)	24.5 (22.2–27.6)
Smoking							
Never	52.8	58.0	46.1	51.5	59.7	49.9	53.8
Former	23.4	24.5	21.3	24.5	22.5	23.9	23.8
Current	22.2	15.9	31.8	22.7	16.2	24.7	21.2
Education							
Primary school completed	24.7	17.0	33.1	21.9	26.0	25.3	23.3
University degree	19.4	28.7	11.9	23.9	17.1	18.3	19.6

Values are expressed as median (interquartile range) or perecnt.

Table 3. Association between consumption of foods of animal origin and risk of HL, NHL, B-cell and T-cell lymphomas in EPIC

	HL			NHL			B-cell lymphomas			T-cell lymphomas		
	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI
Red meat												
<20 g/d	14	1.00		285	1.00		251	1.00		6	1.00	
20–<40 g/d	16	1.23	0.56–2.71	306	0.92	0.78–1.09	277	0.93	0.78–1.11	9	1.20	0.40–3.57
40–<60 g/d	12	1.40	0.57–3.40	260	1.03	0.85–1.24	238	1.04	0.86–1.27	8	1.31	0.41–4.20
60–<80 g/d	9	1.45	0.53–3.93	188	1.04	0.84–1.28	161	0.97	0.78–1.21	12	2.68	0.87–8.31
≥80 g/d	16	1.95	0.73–5.21	228	1.01	0.82–1.26	201	0.97	0.77–1.22	9	1.67	0.49–5.75
p-trend			0.19			0.55			0.99			0.18
Processed meat												
<20 g/d	28	1.00		489	1.00		441	1.00		16	1.00	
20–<40 g/d	16	0.69	0.35–1.36	391	1.05	0.91–1.21	343	1.04	0.89–1.21	11	0.85	0.37–1.92
40–<60 g/d	13	0.93	0.44–1.99	184	0.91	0.75–1.09	166	0.93	0.76–1.13	7	0.88	0.33–2.38
60–<80 g/d	5	0.69	0.24–1.98	95	0.95	0.74–1.21	89	1.01	0.79–1.30	4	1.04	0.31–3.51
≥80 g/d	5	0.71	0.23–2.17	108	1.06	0.82–1.37	89	1.03	0.78–1.36	6	1.14	0.33–3.95
p-trend			0.57			0.82			0.95			0.84
Poultry												
<10 g/d	29	1.00		506	1.00		443	1.00		18	1.00	
10–<20 g/d	21	1.12	0.61–2.06	322	1.04	0.90–1.21	293	1.05	0.90–1.23	10	0.77	0.35–1.73
20–<30 g/d	7	0.65	0.27–1.60	144	1.07	0.88–1.30	130	1.06	0.86–1.31	7	1.05	0.41–2.67
30–<40 g/d	4	0.58	0.19–1.79	103	1.18	0.94–1.48	93	1.18	0.93–1.50	3	0.71	0.20–2.53
40 g/d	6	0.56	0.21–1.46	192	1.24	1.03–1.49	169	1.20	0.99–1.47	6	1.05	0.38–2.87
p-trend			0.12			0.02			0.04			0.97
Offals												
0 g/d	31	1.00		624	1.00		556	1.00		23	1.00	
>0–<1.5 g/d	17	1.62	0.77–3.38	223	0.99	0.82–1.19	193	0.97	0.80–1.19	6	0.71	0.24–2.07
1.5–<3.0 g/d	5	1.07	0.37–3.05	99	0.91	0.72–1.15	86	0.88	0.68–1.13	6	1.19	0.41–3.47
3.0–<4.5 g/d	6	1.15	0.44–3.00	140	1.06	0.87–1.30	128	1.09	0.88–1.34	3	0.60	0.16–2.21
≥4.5 g/d	8	0.85	0.36–2.03	181	0.97	0.80–1.17	165	0.98	0.80–1.19	6	0.67	0.24–1.85
p-trend			0.73			0.98			0.91			0.42
Eggs												
<5 g/day	18	1.00		271	1.00		239	1.00		5	1.00	
5–<10 g/day	7	0.47	0.19–1.21	259	1.05	0.87–1.27	237	1.05	0.86–1.28	7	0.95	0.30–3.02
10–<15 g/day	9	0.92	0.37–2.30	153	1.04	0.83–1.29	128	0.93	0.73–1.18	15	2.97	1.02–8.65
15–<20 g/day	7	0.85	0.31–2.32	147	1.15	0.91–1.44	140	1.18	0.93–1.49	3	0.69	0.16–3.04
≥20+ g/day	26	0.96	0.45–2.06	437	1.06	0.88–1.27	384	1.02	0.84–1.24	14	0.96	0.33–2.81
p-trend			0.42			0.42			0.65			0.55
Milk												
<100 g/d	24	1.00		418	1.00		385	1.00		19	1.00	
100–<200 g/d	13	0.92	0.46–1.84	236	0.95	0.81–1.12	211	0.93	0.78–1.11	4	0.39	0.13–1.17
200–<300 g/d	12	0.86	0.41–1.81	230	0.88	0.74–1.04	206	0.84	0.70–1.01	8	0.75	0.31–1.84
300–<400 g/d	6	1.70	0.66–4.40	90	1.28	1.01–1.62	74	1.14	0.88–1.48	4	1.25	0.40–3.92
≥400 g/d	12	0.88	0.40–1.91	293	0.99	0.83–1.17	252	0.93	0.77–1.11	9	0.75	0.30–1.90
p-trend			0.98			0.64			0.68			0.84

Table 3. Association between consumption of foods of animal origin and risk of HL, NHL, B-cell and T-cell lymphomas in EPIC (Continued)

	HL			NHL			B-cell lymphomas			T-cell lymphomas		
	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI	N	HR	95% CI
Cheese												
<20 g/d	28	1.00		491	1.00		433	1.00		12	1.00	
20–<40 g/d	14	0.76	0.38–1.49	372	1.00	0.86–1.15	336	1.02	0.88–1.19	13	1.35	0.57–3.20
40–<60 g/d	14	1.46	0.71–3.01	188	0.93	0.77–1.13	165	0.93	0.76–1.13	10	1.84	0.70–4.86
60–<80 g/d	6	1.37	0.52–3.62	108	1.11	0.88–1.39	95	1.11	0.87–1.43	4	1.18	0.33–4.22
≥80 g/d	5	1.22	0.42–3.56	108	1.09	0.86–1.40	99	1.17	0.91–1.51	5	1.20	0.34–4.25
p-trend			0.38			0.49			0.33			0.74
Yogurt												
<20 g/d	38	1.00		589	1.00		521	1.00		28	1.00	
20–<40 g/d	5	0.63	0.24–1.64	114	0.98	0.80–1.20	101	0.97	0.78–1.21	6	1.10	0.44–2.74
40–<60 g/d	7	0.95	0.41–2.22	125	1.00	0.82–1.22	111	1.00	0.81–1.23	3	0.67	0.20–2.29
60–<80 g/d	3	0.85	0.25–2.83	68	0.98	0.76–1.27	63	1.03	0.79–1.35	0	—	—
≥80 g/d	14	0.68	0.35–1.32	371	1.02	0.88–1.17	332	1.04	0.89–1.20	7	0.60	0.25–1.46
p-trend			0.30			0.84			0.59			0.12

Hazard ratio was stratified by age in 1-yr categories, centre and sex; adjusted for energy, alcohol, education, fruits, vegetables and smoking.
CI, confidence interval; HR, hazards ratio.

Discussion

In this European prospective cohort study, we did not observe a clear pattern of associations between the consumption of foods of animal origin and risk of lymphomas. However, we noted the associations for specific lymphoma subentities. A high intake of processed meat was related to an increased risk of BCLL and inversely with FL but not to other NHL entities. A high consumption of poultry was associated with an increased risk of B-cell lymphoma, in particular to FL and BCLL.

In the EPIC cohort, a high consumption of red meat was not related to an increased NHL risk. Several studies have previously examined the association between red meat consumption and lymphoma risk, most of which were case-control studies. A cohort study in females reported a statistically significant increase of NHL in women with high red meat intake,[5] a second cohort study reported an increased risk for high consumption of red meat as a main dish,[6] but a third cohort did not observe an association between red meat intake and risk of NHL.[10] Some[7–9] but not other case-control studies[11–18] reported an association with red meat.

Processed meat consumption was not associated with an increased risk of NHL overall, but it was associated with an increased risk of BCLL and a decreased risk of FL. Only two case-control studies observed an increased lymphoma risk with increased processed meat consumption,[9,14] whereas the other studies mentioned earlier did not observe statistically significant associations (reviewed in Ref. 10). However, none of these studies reported on the association between processed meat consumption and lymphoma subentities. Processed meat might contribute to cancer risk by different mechanisms, including formation of *N*-Nitroso compounds or the formation of heterocyclic aromatic amines and polycyclic aromatic hydrocarbons during meat cooking. An inverse association seems to be implausible and might, thus, be more likely due to chance.

In contrast to observations of previous studies, we found an increased risk of B-cell lymphoma, FL and BCLL amongst subjects with high poultry consumption. Neither the two cohort studies[5,6] nor some case-control studies[7,9,11,13,18,19] observed a statistically significant association. The reasons for the observed associations are unclear. Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans were associated with an increased risk of NHL in some epidemiologic studies[27,28] and have been found in poultry meat and milk and dairy products.[29–31] Because this study did not observe an increased risk in association with high milk consumption, the PCDD hypothesis seems to be unlikely. Secondly, poultry may contain oncogenic viruses, especially if the meat is not cooked well. US cohort studies reported a lower risk of NHL in women consuming well-done meats instead of rare or rare-medium meats[5] and a decreased risk of NHL with the more frequent consumption of well-done meat.[6] Oncogenic animal viruses have been suspected as causes of NHL among subjects working with animals or in meat processing,[32] for example, exposure to beef and chicken meat in a European case-control study,[33] but meat consumption has not been connected with transmission of oncogenic viruses yet. Third, chicken and turkeys are often treated with coccidiostats and antibiotics to enhance growth of the animals and to treat and prevent disease in lifestock. The frequency of antibiotic use has been associated with the risk of NHL in some studies.[34,35] However, it is unclear whether the association between antibiotic use and cancer risk is causal and, more importantly, whether antibiotic use in food animals can affect cancer risk

Table 4. Association between consumption of foods of animal origin and risk of B-cell lymphoma subentities in EPIC

	DLBCL		FL		BCLL		MM	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Red meat								
<20 g/d	32	1.00	28	1.00	47	1.00	72	1.00
20-<40 g/d	35	0.87 (0.52–1.44)	33	0.96 (0.57–1.63)	51	0.87 (0.57–1.32)	75	0.88 (0.63–1.23)
40–<60 g/d	32	0.91 (0.52–1.58)	37	1.37 (0.80–2.34)	49	0.99 (0.64–1.55)	58	0.98 (0.67–1.43)
60–<80 g/d	25	0.85 (0.46–1.55)	21	1.04 (0.56–1.94)	34	0.92 (0.56–1.51)	40	0.97 (0.63–1.49)
≥80 g/d	35	0.87 (0.47–1.61)	21	0.85 (0.43–1.68)	53	1.13 (0.69–1.85)	47	0.91 (0.58–1.43)
p-trend		0.69		0.85		0.57		0.86
Processed meat								
<20 g/d	68	1.00	57	1.00	90	1.00	110	1.00
20–<40 g/d	52	1.03 (0.70–1.53)	51	1.18 (0.79–1.78)	62	0.99 (0.69–1.40)	87	0.97 (0.72–1.32)
40–<60 g/d	15	0.60 (0.32–1.10)	21	0.87 (0.50–1.51)	38	1.24 (0.81–1.89)	44	0.87 (0.59–1.28)
60–<80 g/d	9	0.75 (0.35–1.60)	7	0.58 (0.25–1.34)	17	1.20 (0.68–2.12)	32	1.24 (0.79–1.95)
≥80 g/d	15	1.37 (0.68–2.76)	4	0.31 (0.10–0.94)	27	2.19 (1.27–3.77)	19	0.65 (0.36–1.16)
p-trend		0.86		0.04		0.01		0.50
Poultry								
<10 g/d	52	1.00	46	1.00	86	1.00	122	1.00
10–<20 g/d	44	1.15 (0.75–1.75)	34	1.03 (0.65–1.64)	58	1.00 (0.70–1.43)	87	1.30 (0.97–1.75)
20–<30 g/d	22	1.19 (0.69–2.05)	16	1.07 (0.59–1.95)	33	1.24 (0.81–1.91)	29	1.01 (0.66–1.56)
30–<40 g/d	19	1.99 (1.11–3.55)	15	1.60 (0.86–3.01)	19	1.11 (0.65–1.88)	19	1.02 (0.61–1.71)
40 g/d	22	1.15 (0.66–1.99)	29	1.80 (1.07–3.04)	38	1.36 (0.89–2.09)	35	1.03 (0.68–1.57)
p-trend		0.24		0.01		0.14		0.92
Offals								
0 g/d	68	1.00	59	1.00	117	1.00	142	1.00
>0–<1.5 g/d	28	0.91 (0.55–1.52)	23	1.07 (0.61–1.87)	38	0.87 (0.56–1.34)	59	0.98 (0.67–1.42)
1.5–<3.0 g/d	11	0.66 (0.33–1.31)	8	0.75 (0.34–1.66)	20	0.76 (0.45–1.29)	20	0.79 (0.47–1.33)
3.0-<4.5 g/d	17	0.90 (0.51–1.58)	21	1.64 (0.94–2.86)	21	0.74 (0.45–1.22)	36	1.14 (0.76–1.72)
≥4.5 g/d	35	1.25 (0.78–2.00)	29	1.58 (0.95–2.64)	38	0.87 (0.57–1.32)	35	0.86 (0.56–1.30)
p-trend		0.51		0.03		0.32		0.74
Eggs								
<5 g/day	36	1.00	31	1.00	47	1.00	75	1.00
5–<10 g/day	34	0.86 (0.52–1.44)	29	0.78 (0.46–1.33)	48	1.07 (0.69–1.66)	56	0.96 (0.65–1.43)
10–<15 g/day	18	0.69 (0.37–1.30)	16	0.64 (0.34–1.21)	31	1.04 (0.63–1.73)	32	0.94 (0.59–1.51)
15–<20 g/day	22	1.00 (0.54–1.83)	18	0.88 (0.47–1.65)	27	1.09 (0.64–1.86)	30	1.04 (0.64–1.69)
≥20+ g/day	49	0.66 (0.39–1.10)	46	0.73 (0.44–1.21)	81	1.00 (0.65–1.54)	99	1.09 (0.75–1.59)
p-trend		0.13		0.43		0.98		0.50
Milk								
<100 g/d	48	1.00	53	1.00	86	1.00	100	1.00
100–<200 g/d	34	1.20 (0.76–1.88)	28	0.90 (0.56–1.44)	43	0.93 (0.64–1.36)	54	0.86 (0.61–1.21)
200–<300 g/d	30	0.93 (0.57–1.51)	26	0.66 (0.39–1.10)	44	0.86 (0.58–1.28)	53	0.82 (0.57–1.18)
300–<400 g/d	6	0.94 (0.39–2.24)	11	1.25 (0.63–2.47)	7	0.54 (0.24–1.18)	26	1.46 (0.92–2.31)
≥400 g/d	41	1.14 (0.72–1.82)	22	0.51 (0.29–0.90)	54	0.96 (0.66–1.42)	59	0.74 (0.52–1.07)
p-trend		0.74		0.04		0.59		0.38

Table 4. Association between consumption of foods of animal origin and risk of B-cell lymphoma subentities in EPIC (Continued)

	DLBCL		FL		BCLL		MM	
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Cheese								
<20 g/d	62	1.00	50	1.00	85	1.00	116	1.00
20–<40 g/d	49	1.08 (0.72–1.63)	45	1.13 (0.73–1.75)	69	1.09 (0.78–1.54)	85	0.98 (0.72–1.32)
40–<60 g/d	25	0.96 (0.57–1.61)	17	0.75 (0.41–1.37)	40	1.16 (0.76–1.77)	42	0.93 (0.63–1.38)
60–<80 g/d	13	1.10 (0.57–2.13)	11	0.92 (0.45–1.89)	20	1.30 (0.76–2.22)	23	1.08 (0.66–1.77)
≥80 g/d	10	0.85 (0.40–1.83)	17	1.28 (0.65–2.50)	20	1.38 (0.79–2.42)	26	1.26 (0.76–2.07)
p-trend		0.81		0.8712		0.20		0.50
Yogurt								
<20 g/d	75	1.00	68	1.00	112	1.00	128	1.00
20–<40 g/d	16	1.04 (0.60–1.81)	10	0.69 (0.35–1.36)	23	1.03 (0.65–1.64)	24	0.96 (0.61–1.50)
40–<60 g/d	16	1.12 (0.64–1.97)	17	1.08 (0.62–1.88)	24	1.03 (0.65–1.63)	26	0.90 (0.58–1.39)
60–<80 g/d	7	0.81 (0.37–1.80)	6	0.67 (0.28–1.57)	9	0.77 (0.38–1.55)	21	1.44 (0.89–2.33)
≥80 g/d	45	1.04 (0.70–1.56)	39	0.97 (0.63–1.48)	66	0.92 (0.67–1.28)	93	1.12 (0.83–1.50)
p-trend		0.91		0.87		0.56		0.56

Hazard ratio was stratified by age in 1-yr categories, centre and sex; adjusted for energy, alcohol, education, fruits, vegetables and smoking.
CI, confidence interval; HR, hazards ratio.

in humans who consume these foods. In addition, because of the large number of tests we performed in our analysis, chance is also a likely explanation for our unusual findings.

No association between the consumption of eggs and lymphoma risk was observed in the EPIC cohort, confirming the results from previous studies, which were mostly null[6,12,14,15,18] besides one study reporting a statistically inverse[13] and two studies with significantly positive associations.[9,16]

In our cohort, we observed no association of milk consumption and risk of HL, T-cell lymphoma or B-cell lymphoma, but inverse, although not significant associations were seen with FL and MM. Milk and milk products have been included in some studies, which, however, differed by the number of food items included in the analysis ad the categorization of milk products. Our null result is consistent with two[5,6] of three cohort studies.[5,6,36] In contrast, several case-control studies reported a higher NHL risk for high milk consumption,[7,12,14,16] although this was not the case in other studies.[8,9,13,15,18] One might speculate that recall or selection bias could have contributed to this difference in results between cohort and case-control studies. Similarly, the results for dairy products were either null in cohort[5,6] and some case-control[12,14–16] but positive in other case-control studies.[7,9,13]

So far, only few studies have specifically examined the associations of diet with the risk of HL[14] or MM.[14,19,37] One study observed a positive association of liver consumption with risk of MM[14] and in another one, high egg consumption was related to risk of MM,[19] but no other significant association were observed and no conclusions can be drawn so far.

Strengths of our study include the large sample size, the prospective design, and the possibility to partly correct for measurement errors by applying a calibration method, thus, improving the results of the dietary questionnaires. Limitations are the low number of HL and T-cell lymphoma cases and the small number of cases of specific B-cell lymphoma subentities and, thus, limiting the statistical power to detect significant associations. In addition, as mentioned earlier, because of the number of comparisons performed, we cannot exclude chance as alternative (and not unlikely) explanations of our findings. The result for processed meat with a risk increasing association for BCLL and an inverse association with FL brings up the question how far lymphomas subentities are etiologically distinct diseases. So far, no lifestyle factor was found that could clearly be linked to lymphoma risk, and results differ between studies. This might indeed partly be due to distinct morphologic and histological characteristics, and thus, a different proportion of lymphoma subenties in a group of lymphomas may lead to different results.[38] Inconsistent findings between studies might also be due to different population structures, that is, Caucasian versus non-Caucasian populations, but not studies were based on Caucasian populations. Although all studies relied on FFQs to assess dietary intake, they differed in the number of items to assess the intake. This causes a differing depth of covering the consumption of certain food groups that may contribute to inconsistent results between studies.

In conclusion, no clear associations among meat, egg, and dairy consumption were observed in this European cohort. In contrast to previous studies, we found an indication for poultry consumption being associated with the risk of B-cell lymphoma, especially FL and BCLL. The consumption of processed meats was related to an increased risk of BCLL, but to a decreased risk of FL. Because chance cannot be excluded as a plausible explanation of the observed associations, further confirmatory studies are warranted.

Table 5. Association [HR (95% CI)] between consumption of foods of animal origin and lymphoma risk in EPIC—continuous models, observed and calibrated data

		NHL		HL		B-cell lymphomas		T-cell lymphomas	
	Variable	Uncalibrated	Calibrated	Uncalibrated	Calibrated	Uncalibrated	Calibrated	Uncalibrated	Calibrated
Red meat	Per 50 g	1.01 (0.92–1.11)	1.04 (0.83–1.29)	1.20 (0.81–1.78)	1.54 (0.71–3.33)	0.98 (0.88–1.09)	0.96 (0.76–1.21)	1.37 (0.87–2.16)	1.99 (0.78–5.11)
Processed meat	Per 50 g	0.97 (0.87–1.09)	0.96 (0.76–1.23)	0.79 (0.47–1.35)	0.66 (0.22–1.99)	0.98 (0.87–1.11)	0.98 (0.75–1.27)	0.94 (0.54–1.65)	1.12 (0.40–3.15)
Poultry	Per 50 g	1.24 (1.08–1.42)	1.56 (1.26–1.94)	0.53 (0.22–1.29)	0.33 (0.03–3.21)	1.22 (1.05–1.42)	1.64 (1.27–2.11)	1.30 (0.79–2.15)	1.26 (0.39–4.07)
Offals	Per 5 g	0.97 (0.83–1.12)	0.85 (0.63–1.15)	0.29 (0.09–0.99)	0.27 (0.05–1.31)	0.98 (0.84–1.15)	0.88 (0.65–1.19)	0.48 (0.14–1.65)	0.38 (0.04–3.47)
Milk	Per 100 g	1.00 (0.98–1.03)	1.01 (0.96–1.05)	1.00 (0.88–1.14)	0.99 (0.81–1.21)	0.99 (0.96–1.02)	0.99 (0.94–1.04)	1.01 (0.87–1.18)	1.01 (0.79–1.30)
Cheese	Per 50 g	0.99 (0.88–1.10)	1.02 (0.76–1.36)	1.04 (0.64–1.67)	1.14 (0.32–4.10)	0.99 (0.88–1.12)	1.06 (0.78–1.45)	1.24 (0.79–1.92)	1.33 (0.34–5.26)
Yoghurt	Per 50 g	1.02 (0.99–1.05)	1.04 (0.97–1.12)	0.97 (0.82–1.16)	0.92 (0.64–1.34)	1.02 (0.99–1.06)	1.05 (0.98–1.13)	0.89 (0.66–1.19)	0.75 (0.42–1.35)
Eggs	Per 5 g	1.00 (0.98–1.02)	1.01 (0.97–1.06)	1.04 (0.97–1.11)	1.10 (0.95–1.28)	1.00 (0.98–1.02)	1.00 (0.95–1.05)	0.97 (0.88–1.08)	0.93 (0.73–1.18)

Hazards ratio was stratified by age in 1-year categories, center, and sex; adjusted for energy, alcohol, education, fruits, vegetables and smoking.
CI, confidence interval; HR, hazards ratio.

Table 6. Association [HR (95% CI)] between consumption of foods of animal origin and risk of B-cell lymphoma subentities in EPIC—continuous models, observed and calibrated data

		DLBCL		FL		BCLL		MM	
	Variable	Uncalibrated	Calibrated	Uncalibrated	Calibrated	Uncalibrated	Calibrated	Uncalibrated	Calibrated
Red meat	Per 50 g	0.91 (0.68–1.20)	0.88 (0.47–1.62)	0.89 (0.66–1.21)	0.86 (0.43–1.69)	1.03 (0.83–1.28)	1.00 (0.63–1.61)	1.04 (0.85–1.27)	1.04 (0.66–1.65)
Processed meat	Per 50 g	0.99 (0.70–1.40)	1.06 (0.54–2.07)	0.58 (0.38–0.89)	0.36 (0.15–0.87)	1.31 (1.06–1.63)	1.75 (1.11–2.75)	0.80 (0.62–1.03)	0.63 (0.36–1.09)
Poultry	Per 50 g	1.06 (0.69–1.63)	1.25 (0.54–2.90)	1.65 (1.18–2.32)	3.80 (1.32–10.91)	1.54 (1.18–2.01)	2.60 (1.56–4.36)	0.87 (0.59–1.26)	1.02 (0.43–2.43)
Offals	Per 5 g	1.05 (0.73–1.52)	0.91 (0.49–1.68)	1.30 (0.96–1.74)	1.12 (0.65–1.94)	1.00 (0.71–1.40)	0.97 (0.56–1.67)	1.01 (0.74–1.37)	0.60 (0.25–1.43)
Milk	per 100 g	1.00 (0.93–1.08)	1.00 (0.89–1.13)	0.91 (0.83–1.01)	0.89 (0.76–1.05)	0.98 (0.92–1.05)	0.97 (0.87–1.08)	0.95 (0.89–1.01)	0.91 (0.81–1.01)
Cheese	Per 50 g	0.87 (0.61–1.22)	0.83 (0.37–1.88)	1.03 (0.75–1.39)	1.36 (0.59–3.10)	1.06 (0.82–1.37)	1.09 (0.57–2.07)	0.94 (0.74–1.21)	1.06 (0.57–1.99)
Yoghurt	Per 50 g	1.07 (0.99–1.16)	1.16 (0.99–1.36)	1.07 (0.97–1.17)	1.15 (0.94–1.39)	1.01 (0.93–1.09)	0.98 (0.83–1.15)	1.05 (0.98–1.11)	1.11 (0.97–1.26)
Eggs	Per 5 g	0.97 (0.92–1.03)	0.95 (0.84–1.09)	0.98 (0.91–1.04)	0.94 (0.81–1.10)	1.00 (0.95–1.04)	1.03 (0.94–1.13)	1.01 (0.97–1.05)	0.97 (0.87–1.07)

Hazards ratio was stratified by age in 1-year categories, center, and sex; adjusted for energy, alcohol, education, fruits, vegetables and smoking.
CI, confidence interval; HR, hazards ratio.

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Appendix

Food group or subgroup	Including
Red meat	Beef, pork and mutton/lamb
White meat	Equals poultry; including chicken, hen, turkey, duck, goose, rabbit (domestic) and unclassified poultry
Processed meat	All meat products, including ham, bacon, different types of sausages, canned/smoked/dried meat, pate, hamburger and meat balls
Eggs	Eggs and egg products
Milk	Milk, milk beverages
Cheese	Fromage blanc, fresh cheeses and cheeses